TRADE AND GENERIC NAMES OF DRUGS

Neosporin® .....Polymyxin B-Bacitracin-Neomycin

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Primary Hyperparathyroidism

Two Cases—Carcinoma and Adenoma—In a Small Hospital

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SINCE ASKANAZY first described an abnormal parathyroid in 1904,[1] several types of parathyroid disease have been delineated. Because of the protean symptoms associated with it, primary parathyroidism is frequently not considered in diagnosis until the clinical manifestations have completely developed or serum calcium is determined fortuitously, as it was in the two cases here presented. In both cases the patients were admitted for reasons other than primary hyperparathyroidism, and elevated serum calcium levels were discovered on routine admission Chemistry Panel 12 (Technicon SMA 12-60) determinations.

Numerous follow-up studies of primary parathyroid disease make the point that adequate correlation of surgical and pathologic findings during operation can lead to appropriate curative surgical operation.[2-6] All too often this correlation is not made until after the procedure is finished, necessitating further operation later.

This presentation will emphasize routine Chemistry Panel 12 admission analyses[7] and the close correlation of pathologic and surgical findings at the time of the first exploratory surgical procedure for primary parathyroid disease.

Reports of Cases

Case 1. A 68-year-old white woman was admitted to hospital October 1 1969 for elective repair of a right femoral hernia. Constipation and vague bone discomfort had been present for some years. On physical examination no masses were palpated in the neck. A preoperative Panel 12 (SMA 12-60) determination revealed calcium of 16 mg per 100 ml. Phosphorus was 1.9 mg per 100 ml and alkaline phosphatase was 90 millimoles per ml. Blood urea nitrogen was 17 mg per 100 ml and total protein was 6.9 grams, of which albumin was 4.5 grams. Creatinine was 1.9 mg per 100 ml

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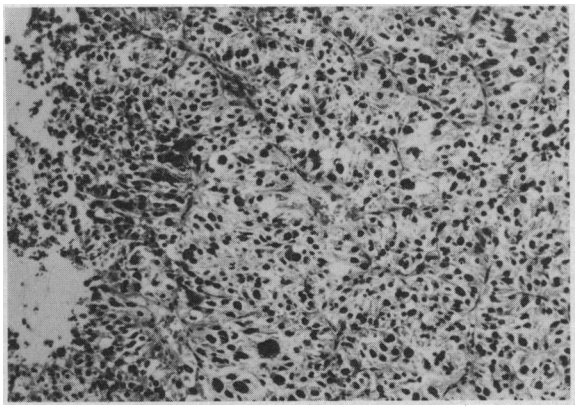

Figure 1.—Parathyroid carcinoma, showing pronounced cellular pleomorphism and trabecular pattern (x250).

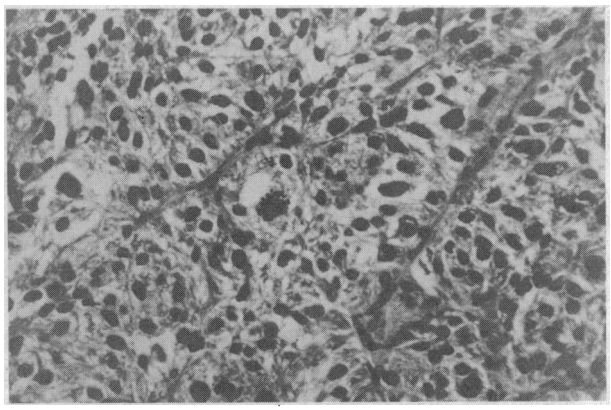

Figure 2.—Parathyroid carcinoma, showing trabecular-glandular pattern with a centrally located abnormal mitotic figure (x400).

and tubular resorption of phosphate was 40 percent (normal 80 to 90 percent). Prednisone was given, 40 mg a day for 5 days. The serum calcium remained elevated at 15.6 mg per 100 ml.

Radiographs of the phalanges revealed subperiosteal resorption in the distal portions of the proximal and midphalanges.

On October 11 an exploration of the neck was performed and a large, rubbery firm, brown-tan mass was found in the left side of the neck, partially compressing the thyroid gland. The tumor was somewhat adherent to the recurrent laryngeal nerve and adjacent tissue, but no frank invasion was noted. A frozen section of the lesion was prepared and the other glands were identified and left intact.

The postoperative course was unremarkable for several days until the serum calcium dropped to 8.4 mg per 100 ml and the patient began to have signs of tetany and paranoid delusions.[8] Treatment was begun immediately with calcium gluconate intravenously and large doses of calcium by mouth, and the serum calcium slowly reverted to normal. The patient was discharged October 19, and all paranoid delusions slowly cleared. Serum calcium remained normal for 12 months, then increased to 13.5 mg per 100 ml.

Pathologist's Report. The specimen consisted of a 5 by 4 cm irregularly shaped, rubbery firm, brown-tan mass appearing roughly encapsulated. Cut section revealed a variegated appearance with areas of yellow-tan blending with brown-tan. Fibrous trabeculae were seen streaking throughout the parenchyma. The total weight of this specimen was 13.5 grams. Microscopically (Figures 1 and 2) the tumor was consistent with parathyroid origin and had a decidedly variegated appearance. Some areas showed fairly regular cells with small, oval, somewhat hyperchromatic nuclei with eosinophilic cytoplasm. Most of the microscopic fields showed large, fibrous septae scattered throughout the parenchyma. These fibrous trabeculae separated the tissue into a glandular, trabecular pattern with individual cells showing pronounced pleomorphism with spindle-shaped nuclei and hyperchromatism containing numerous atypical mitotic figures.[9] Distinct invasion of the capsule was seen in numerous sections.

Case 2. A 68-year-old white woman, a retired school teacher, was admitted to hospital October 28 1969 for evaluation of severe lower extremity cramps, increasing constipation and lethargy. No abnormality was noted on physical examination, and no masses were palpated in the neck. An x-ray film of the chest, sigmoidoscopic examination and radiographic examination of the upper and lower gastrointestinal tract were negative. Panel 12 (SMA 12-60) studies revealed serum calcium of 13 mg per 100 ml. Phosphorus content was 2.3 mg and urea nitrogen 23 mg per 100 ml. Total protein was 6.9 grams per albumin 4.2 grams, alkaline phosphatase 51 millimoles per ml. The serum creatinine was 1.1 mg per 100 ml. Tubular resorption of phosphate (TRP) was calculated at 83 percent by using the formula:

$$\text{Percent TRP} = 100\ \frac{(1\text{-VP} \times \text{SC})^{10}}{(\text{VC} \times \text{SP})}$$

where P = inorganic phosphate concentration (mg per ml)
C = creatinine concentration (mg per ml)
S = serum
V = volume in ml

By the method of Chambers et al,[10] calcium was infused in the amount of 15 mg per kilogram of body weight over a four-hour period. Tubular resorption was measured again and the results showed a flat response with no appreciable change in the TRP rate, indicating an autonomous secretion of parathyroid hormone. Prednisone suppression, 40 mg a day for five days, was carried out and the serum calcium remained elevated at 13.1 mg per 100 ml.

On November 7 1969, surgical exploration of the neck was carried out, and a well encapsulated, chocolate brown mass was removed from the right side of the neck. The mass appeared encapsulated and not adherent to any of the adjacent structures. A frozen section of the lesion and a biopsy specimen and frozen section of a normal parathyroid were prepared. A diagnosis of parathyroid adenoma was then submitted. The postoperative course was uneventful and the patient was discharged November 12 1969. The serum calcium levels thereafter remained within normal limits and the bone discomfort and constipation were relieved.

Pathologist's Report. The first specimen consisted of a well encapsulated brown-tan 3 by 2 cm encapsulated mass weighing 2 grams. On section this specimen was homogeneous and brown-tan. The second specimen consisted of a 0.5 cm portion of yellow-tan, rubbery firm tissue.

On microscopic examination the large mass revealed numerous small, compact cells with eosinophilic, somewhat granular cytoplasm. Numerous capillaries were seen throughout the mass. In one section adjacent to the capsule a normal rim of parathyroid tissue was seen compressed. The mass was completely encapsulated. The second specimen consisted of a regular appearing parathyroid gland with a normal amount of fat.

Discussion

The pathologic changes of primary hyperparathyroidism are of five classes: primary hyperplasia, single adenoma, combined adenoma and hyperplasia, multiple adenomas with or without the association of multiple endocrine adenomas, and carcinoma.[2,5,9,11-16] Primary hyperplasia arising *de novo* or from an unknown stimulus is separated into the water-clear cell type described by Albright[11] and the chief cell hyperplasia more recently described by Cope and others.[2,3,6] The latter has caused much confusion for pathologists because of the similar pathologic appearance of primary chief cell hyperplasia and adenoma. The distinction between these two is, at times, difficult if not impossible when only one gland is examined. Although a functioning adenoma is the most common parathyroid lesion in patients with primary hypoparathyroidism,[9,12,16-19] chief cell hyperplasia with or without association with multiple endocrine adenomas occurs with enough frequency to be of practical importance.[2,9] Chief cell hyperplasia usually involves all parathyroid glands. Therefore, surgical treatment is considerably different than for parathyroid adenoma.[3,20] Because excision of an adenoma results in cure[21,22] and extirpation of anything less than three and one-half glands in primary chief cell hyperplasia will most likely result in continuing or recurrent hyperparathyroidism,[3] it is of utmost importance that the surgeon and pathologist work closely together at the time of the first neck exploration to evaluate all parathyroid glands with biopsy of at least the one other parathyroid than that involved in the lesion.[2] Physical characteristics of the gland —consistency, color and shape and size—are of no appreciable aid in distinguishing between adenoma and chief cell hyperplasia. The microscopic pattern and cytological appearance are frequently very similar in adenomas and chief cell hyperplasia.[14] The presence of a compressed rim of normal appearing parenchyma at the margin of an enlarged gland does give support to a diagnosis of adenoma, but is not a pathognomonic finding as it once was thought to be.[2] Decreased fat content and microscopic nodularity, seen so often in chief cell hyperplasia, can also be of help in the differentiation. If one gland is enlarged and adenomatous, with or without a compressed normal rim of tissue, and the remaining glands are normal or atrophic, adenoma is almost a certainty.[2] Differentiation by this means necessitates exposure of all four glands and biopsy of at least one other gland than the one involved in the lesion, since primary parathyroid hyperplasia usually affects the remaining glands. The possibility of multiple adenomas can be excluded through the careful identification of all glands and biopsy of any suspicious-appearing parathyroids.[14-16,22]

Primary hyperplasia of the clear cell variety is rare. The microscopic and cytological patterns are distinct enough to cause the pathologist no great problems.[9,12,14,23]

The problem of combined adenoma and hyperplasia has recently been studied[5,13,15] and found to be distinguishable from the other causes of parathyroid disease by the procedure just described.

Carcinoma of the parathyroid gland is said to occur in only 3 to 4 percent of all cases of primary hyperparathyroidism.[12,15,24] All parathyroid carcinomas are said to be associated with endocrinologic activity and well marked bone disease,[12,15,24,25] as in Case 1 herein reported. In that case the surgeon suspected the neoplasm was malignant because of the adherence to the recurrent laryngeal nerve. Adherence to surrounding structures is often a helpful clue to malignancy in parathyroid neoplasms.[12,26] It is usually indicative of capsular invasion, which is one of the criteria for diagnosis of parathyroid carcinoma.[9,12] In this respect the criteria for the diagnosis of parathyroid carcinoma parallel those for carcinoma of the thyroid. The neoplasm is so rare that studies of series big enough to permit interpretation of the biological activity of this neoplasm have not been possible. It is thought that the usual spread is first through lymph channels.[12]

Microscopically, parathyroid carcinoma is different from adenoma in a number of ways. As in adenoma, the pattern is variable. Usually, however, capsular invasion is found, although that alone is not sufficient for diagnosis.[9,12] Trabeculation and enlarged atypical mitotic figures are also significant criteria. Mitoses are absent in adenomas and present in carcinomas.[12,24,27] Distinguishing parathyroid carcinomas from atypical adenomas may be extremely difficult. Black and Ackerman[9] restricted the diagnosis of carcinoma to cases in which there is local invasion initially or distal metastasis. We believe that those criteria are too restrictive and that relying entirely on them may give the attending physician a feeling of overconfidence and delay proper treatment. The findings of pronounced cellular pleomorphism, mitotic activity and capsular invasion are more realistic for the diagnosis of parathyroid carcinoma.

Summary

Two cases of primary hyperparathyroidism (adenoma and carcinoma) were discovered serendipitously in a small community hospital by Chemistry Panel 12 (Technicon, SMA 12-60) determinations. A discussion of the various types of parathyroid pathology is presented with emphasis on the correlation of gross, surgical and pathologic microscopic findings at the time of the first exploratory operation. Also stressed is the biopsy of more than one gland to differentiate chief cell hyperplasia from adenoma. The gross and microscopic criteria for the diagnosis of parathyroid carcinoma are reviewed.

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